Human Insulin After 10 Years

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This is the fourth symposium on human insulin to appear in *Diabetes Care*. The first, in March-April 1981, which I edited with Sotis Raptis, appeared just eight months after the first injections of human beings insulin of recombinant DNA origin into humans, and only six months after the first conference on the subject, held in Athens during the annual meeting of the European Association for the Study of Diabetes (1). That symposium included a compilation of the papers presented in Athens that passed the peer-review process. Those papers demonstrated the effects of recombinant human insulin both in vitro and in short-term pharmacological studies in vivo. The studies provided the scientific basis for performance of large-scale clinical studies of recombinant human insulin. Such studies came in short order. The results were presented in June 1982 at a conference held in San Francisco, California, during the annual meeting of the American Diabetes Association. The proceedings of the second symposium on human insulin, after peer review, appeared in the November-December 1982 issue of *Diabetes Care*, just five months after the conference (2). During that same San Francisco meeting of the American Diabetes Association, another conference was held on human insulin produced semisynthetically by enzymatic conversion of pork insulin. In March-April 1983, the results of that conference also were published as a symposium in *Diabetes Care*, edited by John Karam and Donnell Etzwiler (3).

Given this close relationship between *Diabetes Care* and the development of human insulin, as the tenth anniversary of the clinical availability of human insulin approached, it seemed fitting that a special symposium marking the passing of the decade of human insulin be published in *Diabetes Care*. Eli Lilly and Company agreed to sponsor the symposium. To assure an international perspective, Wilhelm Erkelens joined me in selecting authors and topics, which were reviewed and approved by David Robbins, then the Editor of *Diabetes Care*, and by John Galloway of Lilly Research Laboratories, the symposium sponsor. This was all accomplished during the meeting of the International Diabetes Federation in Washington in June 1991. Invitations were sent to prospective authors, all of whom agreed to participate by providing appropriate review manuscripts, with the hope of publication in the summer of 1992. Unfortunately, several manuscripts were delayed. In the interim, the climate and rules regarding journal symposia changed, specifically the guidelines for journal symposia promulgated by the Publications Policy Committee of the American Diabetes Association. In addition, the Editorial Office of *Diabetes Care* moved to Pittsburgh under the editorship of Allan Drash. With the new ground rules and the new editors, all of the invited manuscripts underwent detailed peer review. Dorothy Becker, Associate Editor of *Diabetes Care*, assumed responsibility for shepherding the manuscripts through the peer-review process. The result is a product that we think is informative, albeit delayed. Somehow it is ironic that this inordinate delay contrasts with the incredibly rapid publication of the earlier human insulin symposia in this journal.

Why review human insulin after 10 years, anyway? After all, one could argue that all that really happened was a change of manufacturing source for a product already well established in the management of diabetes mellitus. Admittedly, that change of source assures an unending supply of this vital product. Yet, this alone is an insufficient reason for celebrating human insulin.

Rather, the availability of human insulin stimulated an explosion of research in insulin biochemistry and action, insulin physiology and pharmacology (some aspects of which are reviewed by Lutz Heinnemann and Bernd Richter in this symposium), and in the therapy of diabetes mellitus. Moreover, human insulin was the first product of biotechnology to enter the clinical arena. It served as the stalking-horse for the entire biotechnology explosion. And, it served that role well. Because human insulin was already a well-established therapeutic modality with clinical utility in one of the most common afflictions of humankind, the regulatory hurdles of general safety and efficacy could be readily documented. Consequently, regulatory attention could be focused instead on clarifying whether recombinant products had unique problems that might limit their acceptability for human use. This was accomplished. Clearly, recombinant human insulin made the regulatory process

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FDA, Food and Drug Administration; type I diabetes, insulin-dependent diabetes mellitus; DCCT, Diabetes Control and Complications Trial; type II diabetes, non-insulin-dependent diabetes mellitus.

easier for all subsequent recombinant DNA products.

The U.S. Food and Drug Administration was up to the challenge and performed their task with both diligence and speed. Solomon Sodel, Director of the Division of Metabolism and Endocrine Drug Products, saw approval of human insulin coming and aggressively recruited two senior scientists, a molecular biologist and a chemist, with the requisite expertise to deal with issues unique to recombinant DNA technology. By being involved early in the planning process for recombinant human insulin, the FDA was prepared to act, and did so in an uncharacteristic but scientifically and administratively healthy way. In fact, the New Drug Application for Humulin was submitted in the spring of 1982 and approved in October 1982.

Human insulin also offered the advantage of favorable immunogenicity (as reviewed by Guntrum Schernthaner in this symposium), in comparison to animal insulins, particularly beef insulin and insulins that were not highly purified. Today, in contrast to the early days of my career in diabetes, local insulin allergy and injection site lipoatrophy are virtually unheard of in the U.S. and most developed countries. Insulin purification and the introduction of human insulin have accomplished this. Likewise, immunological insulin resistance, once a rare but vexing problem, simply does not occur any more.

Advances in recombinant DNA technology have permitted the development of other insulin-related molecules. As noted by Ronald Chance and Bruce Frank in this symposium, the switch in human insulin production techniques from separate A-chain and B-chain production with subsequent combination to form insulin to a process involving proinsulin production and cleavage to insulin and C-peptide resulted in availability of both human proinsulin and human C-peptide for testing. Although neither of these may ever become products in the marketplace, studies of them have expanded our understanding of the biology of insulin and metabolic regulation. In addition, in the review by Galloway, the application of site-specific mutagenesis to the insulin and proinsulin molecules has resulted in the development of analogues that may have profound therapeutic applicability in terms of time course of action and solubility of the pharmacologic preparation.

The majority of the articles in this symposium outline the clinical role of human insulin as one component in contemporary management strategies for diabetes mellitus. Over the past decade, those strategies have continued to evolve. Beginning in the late 1970s with the development of self-monitoring of blood glucose and of glycosylated hemoglobin assays, it became possible to design programs for improved glycemic control. In this symposium, Bernie Zinman and Julio Santiago provide interesting commentaries on how they believe insulin therapy for type I diabetes has evolved over the past decade. With the recent presentations and reports from the DCCT (4), documenting that intensive therapy does make a difference in the long-term complications of diabetes, it becomes increasingly important to weigh the comments of these authors, both of whom are DCCT investigators, and gain insight into their management approaches. The DCCT investigators have pointed out that they used unrestrained flexibility and creativity in developing insulin treatment programs unique to the needs of each and every patient. The predictable time course of action and bioavailability of human insulin preparations facilitates the development of those treatment programs. Nevertheless, attainment of overnight glycemic targets, without either hyperglycemia or hypoglycemia, is an area of particular challenge to diabetologists and patients alike. Gerry Bolli has stayed up more nights than perhaps any other investigator studying this area. He and his colleagues review the overnight period for our readers.

One area in which meticulous glycemic control is clearly mandated, and human insulin clearly indicated, is in the management of diabetes during pregnancy. This is true both for diabetes antedating pregnancy and for gestational diabetes. Strategies and success in the management of these clinical conditions are reviewed by John Kitzmiller and Donald Couston, respectively, in this symposium.

Another issue addressed is growth and maturation of children with type I diabetes. This is considered in the article by William L. Clarke, Mary Lee Vance, and Alan D. Rogol.

That leads us to insulin management in type II diabetes, a subject addressed by Veikko Koivisto. In many patients with type II diabetes, the need for insulin may be temporary and/or interrupted, thus increasing the potential risk of immunological side effects. As a consequence, in my view, only human insulin should be used in type II diabetes. Debate continues about the best insulin strategies for type II diabetes, the criteria for initiating insulin therapy for this type of diabetes, and whether insulin therapy should be combined with sulfonylurea therapy to attain glycemic control.

Controversy surrounds the role of hyperinsulinemia, which arises as a consequence of insulin resistance, in the pathophysiology not only of type II diabetes but also of hypertension, dyslipidemia, obesity, and atherosclerosis. Paul Zimmet ably reviews this critical question for our symposium readers.

The last decade of attention toward meticulous glycemic control has brought renewed attention to the major risk that accompanies such control, namely, hypoglycemia. We have come to better appreciate the difficulties wrought by hypoglycemia, the nature of the problems of hypoglycemia unawareness, counterregulatory unresponsiveness, and the impact of therapy on these syndromes. In this symposium, these subjects, as well as potential cognitive problems induced by hypoglycemia, are

discussed by Philip Cryer, Stephanie Amiel, and Edwin Gale.

In addition to the specific articles addressing hypoglycemia, the problem of hypoglycemia unawareness has been mentioned by several other authors. All concur that the attribution of this problem to human insulin per se is groundless. Rather, the introduction of human insulin coincided with the introduction of meticulous glycemic control, and consequent lower prevailing glucose levels and increased hypoglycemic risk. How, then, did such an assertion (that human insulin caused hypoglycemia unawareness) receive the incredible publicity that it has in some countries? First, human and animal insulins are not identical. Therefore, one could argue that there is a basis for a difference in some effects. Second, the popular media and several high-profile lawyers fanned the flames of hypoglycemia hysteria. Third, some investigators became totally committed to advancing the idea that human insulin was patently dangerous. Although the data are scant and unconvincing, the tirades have continued. It is a pity.

Human insulin is not a panacea. It is but one small component of contemporary management, one small step in the advancement of therapy for diabetes mellitus. Where are we going in the future? What lies around the corner? In this symposium, John Galloway addresses advances in insulin. And Chris Saudek, predicts future developments in insulin delivery systems.

Not reviewed here is an even more recent development: therapeutic trials of human insulin as a therapy to prevent type I diabetes (5–7). Two different strategies are being tested, both use first-degree relatives of patients with type I diabetes. These relatives, in a multicenter clinical trial, are being screened for immunological markers of immune-mediated β-cell damage and assessed as to whether they have a higher or lower risk of progressing to clinical type I diabetes with overt hyperglycemia in the next few years. In the higher-risk relatives, the active treatment group will receive parenteral human insulin, which may work by either altering immune responsiveness or by resting β-cells. In the lower-risk relatives with immune markers, the strategy will be to test oral tolerance. Here, relatives will be fed human insulin in capsules, a form in which the insulin is not metabolically active but which may cause a downregulation of the anti–β-cell immune response. Recombinant human insulin, because it is available in unlimited quantities, permits the design and implementation of such therapeutic trials. Could it be that human insulin itself will be the therapeutic agent that eradicates type I diabetes mellitus? If so, how ironic indeed.

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